DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING[1]

DECEMBER 6-7, 1979

The Recombinant DNA Advisory Committee (RAC) was convened for its seventeenth meeting at 9 a.m. on December 6, 1979, in Conference Room 10, Building 31, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland. Dr. Jane K. Setlow, (Chairman) Biologist, Brookhaven National Laboratory presided. In accordance with Public Law 92-463 the meeting was open to the public, except for the review of proposals involving proprietary information as the last item of business on December 7, 1979.

Committee members present for all or part of the meeting were:

Dr. Abdul Karim Ahmed; Dr. David Baltimore; Dr. Winston Brill; Dr. Francis Broadbent; Dr. Allan Campbell; Mrs. Zelma Cason; Dr. Richard Goldstein; Dr. Susan Gottesman; Dr. Jean Harris; Ms. Patricia King; Dr. Sheldon Krimsky; Dr. Werner Maas; Dr. James Mason; Dr. Elena Nightingale; Dr. Richard Novick; Dr. Samuel Proctor; Mr. Ray Thornton; Dr. LeRoy Walters; Dr. Luther Williams; Dr. Frank Young; Dr. Milton Zaitlin; and Dr. William J. Gartland, Jr., Executive Secretary.

A Committee roster is attached. (Attachment I)

The following ad hoc consultants to the Committee were present:

Dr. Kenneth Berns, University of Florida
Dr. Roger Herriott, Johns Hopkins University

The following non-voting members and liaison representatives were present:

Dr. George Duda, Department of Energy; Dr. Herman Lewis, National Science Foundation; Dr. Melvin Myers, National Institute for Occupational Safety and Health; Dr. Mariano Pimentel, Department of Interior; Dr. Jane Schultz, Veterans Administration; Dr. Sue Tolin, United States Department of Agriculture; and Dr. William J. Walsh, III, Department of State.

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[1]The RAC is advisory to the NIH, and its recommendations should not be considered as final and accepted. The Office of Recombinant DNA Activities should be consulted for NIH policy on specific issues.

Other National Institutes of Health staff present were:

Dr. Stanley Barban, NIAID; Dr. W. Emmett Barkley, NCI; Mrs. Betty Butler, NIAID; Dr. Irving Delappe, NIAID; Dr. John Irwin, DRS; Dr. Richard Krause, NIAID; Dr. Malcolm Martin, NIAID; Dr. Elizabeth Milewski, NIAID; Dr. Stanley Nagle, NIAID; Dr. John Nutter, NIAID; Mr. Richard Riseberg, OGC; Dr. Wallace Rowe, NIAID; Ms Janet Sobell, OD; Dr. Bernard Talbot, OD; Dr. George Vande Woude, NCI; and Dr. Burke Zimmerman, OD.

Others in attendance for all or part of the meeting were:

Dr. John Adams, Pharmaceutical Manufacturers Association; Dr. E. A. Agostine, Pfizer, Inc.; Dr. Rosanne Apfeldorf, Occupational Safety & Health Administration; Dr. Howard L. Bachrach, Department of Agriculture; Mr. Dave Beddow, O'Melving & Myers; Dr. Queta Bond, National Academy of Sciences; Dr. K. C. Bora, Health & Welfare, Canada; Dr. Jerry Callis, Department of Agriculture, Plum Island; Dr. Ronald Cape, Cetus Corporation; Mr. Jeffrey Christy, Blue Sheet; Mr. Leslie Dach, Environmental Defense Fund; Dr. Otis P. Daily, Navy Medical Research Institute, Bethesda; Mr. David Dickson, Nature; Dr. Clarence Grogan, Department of Agriculture; Dr. Philip Harriman, National Science Foundation; Dr. Zsolt Harsanyi, Office of Technology Assessment; Ms. Robin Henig, BioScience; Dr. Paul Hung, Abbott Research Laboratories; Dr. Evelyn Hurlburt, Johns Hopkins School of Hygiene; Dr. Dorothy Jessup, Department of Agriculture; Dr. I. S. Johnson, Eli Lilly & Company; Dr. Attila I. Kadar, Food and Drug Administration; Mr. Alan Kaplan, Attorney, Washington, D.C.; Dr. Charles C. Kimble, Food & Drug Administration; Dr. Gretchen Kolsrud, Office of Technology Assessment; Dr. M. A. Levine, Environmental Protection Agency; Dr. David Logan, Occupational Safety & Health Administration; Dr. Robert W. M. McKinney, Enviro Control, Inc.; Dr. James McCullough, Library of Congress; Dr. Charles S. Marwick, Medical World News; Dr. DeLill Nasser, National Science Foundation; Dr. William O'Neill, Poly-Planning Island; Dr. Seth Pauker, Occupational Safety & Health Administration; Dr. Gerald G. Platt, Department of Agriculture; Ms. Maria Recio, Business Week; Dr. Michael Ross, Genentech, Inc.; Dr. Frady T. Saunders, M.D. Anderson Hospital; Dr. Anne Schauer, United States Department of Agriculture; Dr. Nelson Schneider, E. F. Hutton; Mr. H. M. Schmeck, New York Times; Dr. Brian Sheehan, Genentech. Inc.; Dr. M. H. Silverstein, Department of Agriculture; Dr. Vincent Simmon, Genex; Dr. Louis Slesin, Natural Resources Defense Council; Dr. Moselia Sohaechter, American Society for Microbiology; Dr. Stephanie Soucek, Occupational Safety & Health Administration; Dr. J. R. Swarz, Staff, United States Senate; Dr. Gloria Troendle, Food & Drug Administration; Dr. Michael Trudeao, National Science Foundation; Dr. Susan Wright, University of Michigan; and Dr. W. P. Young, Eli Lilly & Company.

I. CALL TO ORDER AND OPENING REMARKS

Dr. Jane Setlow, chairperson, called the meeting to order at 9 a.m., December 6, 1979. Dr. Setlow began the meeting by introducing a new Recombinant DNA Advisory Committee (RAC) member, Dr. Jean Harris. She also introduced two ad hoc consultants, Dr. Roger Herriott and Dr. Kenneth Berns.

II. MINUTES OF SEPTEMBER 6-7, 1979 MEETING

The RAC reviewed the minutes of the previous meeting (tab 795). Dr. Walters said that he had discovered one substantive error which he believed to be typographical; on page 35 in line 19: "Section 1e" should be "Section 1c." He added that he had some minor editorial suggestions to submit to the Executive Secretary. Dr. Walters then moved approval of the Minutes. Dr. Ahmed noted that in the vote on the E. coli K-12 proposal several individuals had requested that their vote be recorded; those names had not been included in the Minutes. Dr. Ahmed added that the names of people assigned to working groups should be recorded in the Minutes. Dr. Wright, a member of the public, said that in the previous meeting she had questioned Dr. Fredrickson regarding NIH's position on mandatory regulation of industry, and that neither her question nor his response had been included in the Minutes. She requested that this exchange be included. With incorporation of these changes, the Minutes were approved by a vote of fourteen for, none opposed and one abstention (Ms. King).

III. STATUS OF RAC RECOMMENDATIONS MADE AT SEPTEMBER 1979 MEETING

Dr. Setlow delivered an update on the the status of the major actions recommended by the RAC at the September 1979 meeting. She stated that tab 796 is the text of a notice that appeared in the Federal Register on November 30, 1979. The notice publishes for 30 days of comment the proposed revised Guidelines incorporating actions recommended at the September 1979 meeting. Following this comment period, a final decision on these actions will be published.

Dr. Setlow noted that Dr. Fredrickson's proposed decision departs somewhat from the E. coli K-12 proposal as recommended by the RAC in September. In Dr. Fredrickson's proposal, most E. coli K-12 manipulations are not exempt from the Guidelines; registration and review by NIH would not, however, be necessary for these experiments. She noted that Dr. Fredrickson accepted P1+EK1

containment conditions and the requirement that these experiments must be registered with the local IBC. Prior review and approval of experiments by the IBC would be required when there is attempted efficient expression of a gene coding for a eukaryotic protein. Dr. Talbot said that Dr. Fredrickson welcomes individual written comments by RAC member.

Dr. Setlow said that the RAC should specifically consider three items in the proposed revised Guidelines. The first is how the Guidelines should treat single stranded Ff phages. Dr. Setlow requested that the "Phage" Subcommittee consider this. The second question is whether it is appropriate for HV1CV to be substituted for EK1CV in Section III-A-2-a, "Viruses of Eukaryotes." She noted that, at the moment, the only non-E. coli systems certified as HV2 are yeast systems. Dr. Setlow asked Drs. Elena Nightingale and Winston Brill to consider this question. The third question concerns the need for prior NIH approval for lowering containment levels for characterized clones or purified DNA. Dr. Setlow appointed Drs. Ahmed, Novick, and Williams, to consider this issue. For each of these 3 items, she requested that the groups prepare recommendation for publication in the Federal Register prior to the March 1980 RAC meeting, if they feel a change is desirable.

In response to a question from Dr. Ahmed, Dr. Talbot stated that experiments exempt under the Guidelines need not be registered with the local IBC. He added that this issue is one of the meeting's agenda items. In response to a question from Dr. Goldstein, Dr. Talbot cited the decontamination requirements of P1 containment.

IV. REQUEST FOR EXCEPTION TO A PROHIBITION TO DEVELOP FOOT AND MOUTH DISEASE VACCINE

Dr. Setlow then began discussion of a request from the Department of Agriculture Research Center at Plum Island for an exception to the prohibition against cloning DNA from a Class 5 pathogen (tab 763, 764, 765, 782, 783). Dr. Baltimore described the historical background and the virology of Foot and Mouth Disease (FMD). He said that some countries have chosen to vaccinate animals while others have not. The United States attempts to control Foot and Mouth Disease by rigorous quarantine measures. In the U.S., the virus is studied only at the Plum Island Animal Disease Center. The proposal before the RAC is an attempt to employ a new approach to vaccine development. FMD virus is a picornovirus with a genome composed of single strand RNA. The

work as proposed will be a collaboration between Genentech, Inc., and the Plum Island Animal Disease Center. Workers from Genentech will reverse transcribe the FMD genome on Plum Island. Fragments of reverse transcription products will be cloned and tested for infectivity before removal from Plum Island.

Dr. Baltimore said that provided no potentially infectious material is removed from Plum Island the plan seems innocuous. To be certain that no full length pieces are produced, Dr. Baltimore suggested the RAC could specify that any clone removed from Plum Island contain less than five thousand bases of FMD related DNA. Dr. Baltimore moved approval of the proposal with this added caveat.

Dr. Ahmed asked how infectivity of reverse transcribed segments will be tested. Dr. Bachrach said that infectivity is tested by injection of the material into cattle, swine, and calf thyroid tissue cultures. Dr. Ross of Genentech said only DNA will be removed from Plum Island.

Dr. Goldstein asked for information concerning the incidence of FMD. Dr. Bachrach responded that there have been nine outbreaks of FMD in the United States, the last in 1929. Dr. Goldstein then asked why the clones are being moved to Genentech. Dr. Ross responded the work at Genentech, which includes sequencing of the clones requires a good deal of time. Dr. Goldstein said that sequencing is not a particularly difficult operation. He questioned whether movement of these clones from one place to another is necessary. Dr. Baltimore responded that the construction of an expressing clone involves state of the art recombinant DNA work. He said that a recombinant DNA laboratory could be established on Plum Island, but he did not feel that it should be required.

Dr. Goldstein stated that there are defective viruses missing numerous genes which can be rescued. He said that limitation on size does not neccesarily allay his concerns on infectivity or potential infectivity. Dr. Baltimore asked Dr. Goldstein to present a scenario for the rescue of a clone which contains 5000 base pairs of a picornovirus. Dr. Young noted that cases of recombination between plasmids with overlapping segments have been demonstrated. He suggested the RAC might want to restrict the experimental protocol to preclude the use of overlapping sequences and multiple plasmids.

Dr. Young then requested a description of the containment procedures to be followed in shipping the DNA from Plum Island to the West Coast. Dr. Callis, Director of Plum Island Animal Disease Center, responded that after the material is safety tested, it will be placed in a polyethylene bag which will be placed inside of a metal container containing sodium hydroxide. This container will be sealed and will be placed inside another can which will also be sealed. That will be placed inside of a thermos container which will be placed inside of a wooden box which would be couriered to California.

Dr. Campbell said that a situation where all of the pieces of FMD DNA could come together should be avoided, although a barrier to spread exists in getting FMD genetic information from E. coli into a mammalian cell. Dr. Baltimore pointed out that should the virus escape, an established procedure for dealing with this situation exists. Dr. Campbell said that he would be more comfortable if the material removed from Plum Island had zero probability of harm.

Dr. Goldstein asked whether FMD could be packaged in a phage coat. Dr. Baltimore stated that it could be packaged. Dr. Goldstein then suggested that the RAC consider approving only that part of the proposal dealing with work at Plum Island, i.e., Stage I.

Dr. Bachrach then explained some of the biology of FMD. He said that the genome could be cleaved yielding an L and an S fragment. He said that as an alternative pathway the protocol could work with the L fragment. Dr. Bachrach said that the L fragment is non-infectious in mammalian cells.

Mr. Thornton said that he had problems with the material being shipped by courier to California and subsequently placed in a P1 laboratory. He said that either the material is not dangerous, or it is infectious and should be handled as FMD virus. He proposed that the RAC accept Dr. Goldstein's suggestion of approving Stage I. Dr. Young asked if multiple experiments had demonstrated that the L fragment is not infectious. He said that if this is the case, the L fragment would provide a very elegant biological containment. Dr. Bachrach said that use of the L fragment is not part of the proposed protocol but rather an alternative pathway. Dr. Baltimore stated that he would be willing to accept as an amendment to his motion that approval be recommended for the cloning of reverse transcripts from the L fragment.

Dr. Goldstein asked Dr. Callis to discuss the problem of vaccine efficacy. Dr. Callis responded that approximately 800 million doses of vaccine are used yearly worldwide. Dr. Goldstein asked if antigenic drift occurs in FMD. Dr. Callis responded that a drift does occur but not to the extent as in influenza. He said there are seven immunological types of FMD and approximately sixty-five subtypes.

Dr. Ahmed then proposed an amendment to Dr. Baltimore's motion. He suggested the addition of a requirement that no material be removed from Plum Island until all the relevant data have been reviewed by the RAC following review by a working group. Dr. Young suggested approving the project in principle with the qualification that the data be reviewed before the material is transported from Plum Island. Dr. Ahmed asked whether the subgenomic fragments would be considered a Class 5 agent. Dr. Young responded that organisms are classified as pathogens in their natural state. Non-infectious fragments would not be equated with a Class 5 agent.

Dr. Novick asked whether there could be recombination between FMD virus and related viruses that are not Class 5 agents. Dr. Baltimore agreed that it could occur but said that such an event is highly unlikely. Dr. Bachrach said that there is evidence of cross encapsidation but not of recombination between bovine enterovirus and FMD.

Dr. Gottesman said that the FMD proposal could be broken down into three issues. She suggested that the RAC deal with them and vote on them one-by-one. She said that the first issue is the making of the clones on Plum Island. She noted that there appears to be a agreement on this phase. The second issue deals with what further approval is required before the clones are to leave Plum Island. She suggested that the RAC could review the data on the L fragment, the data on the clones which will be generated on Plum Island and the results of infectivity testing. The third issue is the appropriate containment for the work in California. Dr. Ahmed said that he was not comfortable with only a subcommittee reviewing the data.

Dr. Nightingale noted this is the first request for an exception to a prohibition. She expressed concern that one of the reasons given for removing the clones from Plum Island was the convenience of the researchers. Dr. Ross responded that it is not simply a question of inconvenience of the researchers. He said that all

the resources available in a modern molecular biology laboratory are necessary to characterize the clones. An enormous expense would be involved if these resources had to be moved to Plum Island.

Dr. Krimsky asked for more background on the conventional methods of producing FMD vaccine. He asked whether the recombinant technique would be safer than conventional techniques for producing vaccine. Dr. Callis responded that of the estimated 800 million doses of vaccine produced annually, the virus in about 300 million doses is produced in explants of bovine tongue epithelium. Virus for about 500 million doses is produced in tissue culture systems. Dr. Callis said that in order to produce vaccine by this method, enormous quantities of virus must be produced with the attendant containment problems. He suggested that recombinant technology could produce vaccine at considerably less expense as a stable product, without risk of the virus escaping from factories. Many outbreaks today result from incompletely inactivated vaccine or escape of the virus from factories.

Dr. Berns asked Dr. Callis to explain how the vaccine would be used in case of an outbreak. Dr. Callis responded that the policy on FMD and other infectious foreign animal diseases is to eradicate them should they enter the U.S. In the case of FMD, eradication has been attempted by slaughter and burial or incineration of all infected and exposed animals. USDA policy for control of FMD depends on eradication, including the application of vaccines. He said that in an outbreak the vaccine would be administered to all susceptible animals within a twenty-five mile radius. Dr. Berns asked what role timing plays in the ring containment procedure. Dr. Callis responded that time is of essence. Dr. Novick said that the hazard of using a subgenomic fragment is infinitesimal in comparison to using the whole virus to produce vaccine and the RAC should permit the research to proceed.

Dr. Goldstein said he thought the project a worthy one. However, he said he is concerned because the project involves a company which has been in open violation of the NIH Guidelines. Dr. Ross responded that Genentech is not now nor ever has been in open violation of the Guidelines. Dr. Krimsky asked Dr. Gartland if he could provide any additional information. Dr. Gartland stated that under the 1976 Guidelines the only scale-up prohibition was against scale-up of recombinant DNAs "known to make harmful products." He said that the Genentech IBC made a judgement that the A chain and B chain insulin recombinants were not known to

make harmful products and Genentech began a scale-up in October 1978 under the 1976 Guidelines. On December 22, 1978, the NIH revised the Guidelines, and these revised Guidelines went into effect on January 2, 1979. The revised Guidelines contain a more stringent standard for scale-up including approval by the Director, NIH. Dr. Gartland said that Genentech has stated they have not been in violation of the Guidelines.

Dr. Callis stressed the point that the USDA has a committee, the Vectors Committee, which regulates materials shipped off Plum Island. He said the material to be shipped off the island will be subjected to stringent tests for infectivity. Dr. Campbell asked whether every shipment off of the Island is approved by the committee. Dr. Callis said that it is.

Dr. Gottesman then proposed the following four-part motion:

(1) That the RAC approve the formation of recombinants between Foot and Mouth Disease Virus and plasmid pBR322 as outlined in Stage I of the scientific plan of document #763, to take place at Plum Island;

(2) That a working group be formed to examine data on the infectivity of sub-genomic portions of the Foot and Mouth Disease Virus and to examine the testing data and infectivity of the clones produced on Plum Island;

The collection of clones to be approved for removal from Plum Island shall not contain among them the full genome of the Foot and Mouth Disease Virus;

The working group shall:

(a) be empowered to approve the continuation of the experiments through Stage II and Stage III,

or, alternatively

(a') report back to the full RAC on the infectivity data. The RAC will then consider approval for further stages of the experiment.

and

(b) recommend to the RAC procedures for continued monitoring of these experiments.

(3) That experiments with the Foot and Mouth Diesease clones at Genentech be carried out at P3+EK1 or P2+EK2 containment;

(4) Stage IV experiments (isolation of clones from other FMD type viruses) shall also be examined by the Working Group before removal of clones from Plum Island,

or, alternatively

(4') Stage IV experiments shall not be begun before review of results of Stages I-III by the RAC.

Dr. Gottesman moved Part 1 of her motion and Mr. Thornton seconded the motion. The RAC recommended approval of Part 1 of the motion by a vote of 17 in favor, none opposed, and one abstention.

Dr. Gottesman discussed Part 2 of her motion. Dr. Young suggested a preamble to Part 2 of the motion:

"While the RAC approves the entire project in principle, it is recognized that data from the first phase must be evaluated prior to removal of any clones from Plum Island. Accordingly...."

Dr. Gottesman accepted this amendment.

Dr. Zaitlin said he thought the sense of the discussion was that the clones should not contain collectively as well as individually the complete genome. Dr. Gottesman agreed and modified that section of the motion to read:

"The collection of clones to be approved for removal from Plum Island shall not contain among them, collectively or individually, the full genome of the Foot and Mouth Disease Virus."

Dr. Harris said that she was strongly predisposed toward alternative 2a' of Dr. Gottesman's motion. Dr. Baltimore felt that the RAC should not constantly interpose itself in the process and engender long delays. He favored alterative 2a. Dr. Goldstein said that the RAC by passing the first part of the motion has already given a strong go-ahead, but that it has a responsibility to oversee the project.

Dr. Mason said that the RAC could delegate responsibility to a working group with the provision that if any concerns arise the issue be returned to the RAC. Dr. Walters suggested the RAC delegate authority to the working group with the provision that the working group report to the RAC by mail. Dr. Goldstein said that the working group should report back to the full RAC in session. Dr. Harris suggested that the working group be empowered to authorize the work to proceed in the absence of any data to the contrary. Dr. Williams said that the issues and the data to be evaluated are relatively straightforward and simple, and appointing a working group with the representative expertise would be a reponsible procedure. A straw vote was taken on whether the RAC preferred alternative (a) or alternative (a') of Part 2 of Dr. Gottesman's motion. Nine members of the RAC preferred alternative (a), nine members preferred alternative (a').

Dr. Gottesman moved Part 2 of the motion with alternative a' including the modifications previously suggested by Drs. Young and Zaitlin which she had agreed to. Dr. Campbell asked whether the motion would permit the working group to recommend at the next RAC meeting that future considerations be delegated to the working group. Dr. Gottesman and Dr. Young agreed that the RAC might proceed in that manner. Dr. Campbell stated that it was the sense of the RAC that this motion constituted the "major action" and that future recommendations of the RAC approving future recommendations of the RAC approving further stages of the experiment would be "minor actions." The motion was accepted by a vote of thirteen in favor, four opposed, and one abstention.

Dr. Gottesman then moved part three of her motion, and it was seconded by Dr. Walters. Dr. Campbell said he wanted to amend containment conditions to P1+EK1. This was seconded by Dr. Baltimore. Dr. Gottesman said that the question of whether there is any possibility of the clones recombining with related viruses must be considered. Dr. Baltimore said that the postulate of recombination between two disparate animal viruses has no precedent. Dr. Krimsky asked if USDA has any responsibility once the material from Plum Island arrives at another facility. Dr. Callis answered the Vectors Committee evaluates the experimental protocol, the qualifications of the personnel, and the adequacy of the facilities where the work is to be done.

Mr. Thornton said that he cannot reconcile the idea of a container being courierred across the country and then the contents being used at P1+EK1 conditions. Dr. Baltimore said that it was his

impression that Dr. Callis described a set procedure for shipment of materials from Plum Island and not an evaluation of the hazard. Dr. Callis said he had described a set procedure for shipment of a viable agent. He said that non-infectious material can be shipped according to NIH shipping procedures.

Dr. Walters moved the following substitute motion:

> "That the entire matter of the appropriate physical and biological containment levels for Stages II and III to be performed at Genentech be referred to the working group that will report back to the RAC."

Dr. Baltimore said that no purpose would be served by relegating the issue to a working group. Dr. Brill suggested that the RAC might require that the transported materials be opened under P3 conditions. Once the canister is opened, P1 conditions would be used. The Walters' motion was denied by a vote of five in favor, twelve opposed, and one abstention. The RAC then voted on the Campbell amendment to substitute P1+EK1 for P3+EK2 or P2+EK2. The amendment was accepted by a vote of nine in favor, seven opposed and two abstentions. Dr. Setlow then called for a vote on Part 3 of the motion as amended by Dr. Campbell's amendment.

> "That experiments with the Foot and Mouth Disease clones at Genentech be carried out at P1+EK1 containment."

The motion was accepted by a vote of nine in favor, seven opposed, and two abstentions. Dr. Goldstein requested that his vote be recorded as opposed.

Dr. Gottesman then presented Part 4 of her motion. It was agreed that this portion does not have to be dealt with under the present situation.

Dr. Setlow appointed a working group composed of Drs. Baltimore, Young, Campbell, and Gottesman.

V. PROPOSED EXEMPTION OF EXPERIMENTS IN TISSUE CULTURE

The RAC began consideration of tab 789. Dr. Talbot said that this is a major action which has not appeared in the Federal Register for public comment in connection with this meeting; therefore, final action by the RAC on it cannot occur at this meeting. Dr. Rowe questioned this since it was part of the major actions published for comment in the Federal Register two

meetings ago. Dr. Talbot, however, noted that two meetings ago the RAC made their recommendation and the Director, NIH, subsequently promulgated his decision on this issue. Dr. Talbot said that if further revision is to be recommended by the RAC, the proposed revision should first appear in the Federal Register for a new period of public comment.

Dr. Rowe said he had suggested at the May 1979 meeting that experiments involving insertion of recombinant DNA molecules into tissue culture cells be exempted from the Guidelines, provided that if eukaryotic viral genes were involved, less than one-fourth of the total viral genome could be used. He said that in the discussion at the May 1979 RAC meeting, rather than press the issue of whether one-fourth of a virus could generate a biohazardous agent, he deleted this section from the proposal so that the final recommendation as passed by the RAC and subsequently accepted by the Director, NIH, allows no component derived from a eukaryotic virus under this exemption. Dr. Rowe now polled several eminent virologist and forwarded their responses to the RAC. They favored allowing one-fourth or less of the genome of a eukaryotic virus within this exemption. Dr. Novick stated that at a previous meeting Dr. Baltimore produced a scenario in which two ends of an RNA tumor virus in the right context could replicate. Dr. Baltimore said that he had said the ends of the viral genome have all the signals required for replication, but reverse transcriptase is also required and must be provided by a helper virus. Dr. Novick asked if rescue of defective viruses was uncommon. Dr. Baltimore said that it is not uncommon in the laboratory, but the co-maintence of a defective and non-defective virus in nature is very rare.

Dr. Gottesman said that an issue is whether the addition of one quarter of one virus, one quarter of a second virus, and one quarter of a third virus to the same culture should be permitted under this exemption. She said the RAC specifically required those situations be reviewed on a case-by-case basis. Dr. Gottesman said that the tK piece of Herpes Simplex Virus is very useful and that this situation should be handled separately. However, all viral combinations should not be permitted.

Dr. Baltimore said he would like to modify Dr. Rowe's proposal as he finds the restriction to one quarter of a virus to be artificial and extremely low. He proposed to add to the exemption:

> "Or that contain a demonstrably defective genome of a eukaryotic virus."

Later, however, Dr. Baltimore said that he was pursuaded that it is counterproductive to set up a criterion such as "demonstrably defective." He preferred Rowe's proposal, with a change of one-fourth to two-thirds.

Dr. Gottesman said that the tissue culture exemption as passed by the RAC did not include viruses, as recombinant DNA in the absence of a viral vector would not escape from tissue culture. She said that in the cases being discussed, the virus is capable of rescue. She noted that many of these experiments are presently allowed under specified containment conditions. She said she felt this proposal to be a big step and not entirely appropriate. Dr. Young asked why Dr. Baltimore preferred an exemption rather than a requirement for P1 containment. Dr. Baltimore said he wouldn't want to defend exempt as opposed to P1 because tissue cultures are normally handled under at least P1 conditions. Dr. Rowe said that he would defend an exemption with tissue culture cells. He said exemption would eliminate a superstructure of administrative control which is unnecessary.

Dr. Berns asked whether this exemption includes experiments in which the recombinant genome will be rescued. He questioned whether such an experiment should require a higher level of containment.

Dr. Berns said that the difference between two-thirds and one-fourth of a genome is not meaningful as in both cases the virus is an absolute defective requiring rescue with helper virus. Dr. Goldstein agreed saying that in some cases less than 25% of the viral genome can be rescued very readily.

Dr. Setlow said she would appoint a small working group of Drs. Baltimore, Berns, and Setlow to draft a proposal for publication in the Federal Register for the March 1980 meeting.

VI. PROPOSED CONTAINMENT FOR CLONING TUMOR VIRUS GENES

Dr. Berns introduced the discussion of tab 774/11 and 784-788. This issue was brought to the RAC by Dr. Stuart Newman of New York Medical College. Dr. Berns said Dr. Newman raises the question of whether insertion of pieces of the polyoma genome into a recombinant DNA molecule enhances tumoriginicity. Dr. Berns said the second question Dr. Newman asks is whether E. coli K-12 producing human eukaryotic protein might trigger an autoimmune disease. Dr. Berns noted that letters from several eminent immunologists suggesting that that would not be the case have been presented to the RAC.

Dr. Berns discussed the results reported in Table 2, page 1141 of tab 787. Dr. Berns said there is no statistically significant difference in the tumorigenicity of the recombinant molecule and purified polyoma DNA. No obvious enhancement of tumorigenicity occurs when the polyoma genome is ligated into a plasmid or phage DNA. The data do not support Dr. Newman's contentions.

Dr. Berns moved that Dr. Newman's request (i.e., that "containment for tumor virus gene splicing experiments be raised to P4+EK2") be denied. The motion was accepted by a vote of thirteen in favor, two opposed and two abstention. Dr. Goldstein requested that he be recorded as voting opposed.

VII. PROTOCOLS REQUIRING ASSIGNMENT OF CONTAINMENT LEVELS

A. Request to use parvovirus H-1 as a vector.

Dr. Baltimore began the presentation of tab 769 and 791. Dr. Solon Rhode of the Institute for Medical Research at Bennington, Vermont, requested permission to insert the Herpes Simplex thymidine kinase (tK) gene into parvovirus H-1. He said H-1 has no known pathogenicity except for newborn rodents. Dr. Rhode intends to establish the defective virus in tK minus hamster cells with a helper H-1 virus. Dr. Baltimore said H-1 becomes defective when a segment is deleted and replaced with Herpes tK gene. He said Dr. Rhode believes that if the tK gene functions the whole system will become tK plus and virus will be produced in the presence of helper. Dr. Rhode would then seek recombinants independent of helper virus with the idea that if a mammalian origin of DNA replication is incorporated into the viral genome, replication would begin at the mammalian origin and the production of virus would not require any trans function. Dr. Berns noted that Dr. Rhode never mentions the source of the DNA being shotgunned. Dr. Gottesman said that this proposal is basically a request for use of H-1 virus as a vector system for cloning in animal cells. She stated that little is known about the host range and the replication of this virus. Dr. Berns said that Dr. Rhode requests P2 physical containment for this experiment. However, Dr. Berns said he thought P3 containment was more reasonable. Dr. Novick moved that this request be denied, but then amended his motion to permit the experiment at P3.

Dr. Walters said that this discussion was very difficult for a lay person to understand. He asked whether the investigator might specify the source of the DNA. Dr. Goldstein suggested

that the RAC request further clarification. Dr. Martin said no arguments had been advanced to explain the hypothetical dangers which might be present in this case. He said this virus requires a helper; if there is no helper present the recombinant virus will not leave the laboratory. Dr. Berns responded that there are defective viruses which survive in nature.

Dr. Walters suggested that action on the proposal be deferred because the investigator has not explained the protocol clearly enough. Dr. Krimsky pointed out that the RAC had asked initiators of proposals to write a statement in a form that would be reasonably understood by people who are not experts in the field.

Dr. Baltimore moved that the RAC accept the proposal at P2. The RAC disapproved Dr. Baltimore's motion by a vote of three in favor, eleven opposed, and four abstentions. Dr. Young then moved that this submission be disapproved with advice that the investigator submit a complete, detailed MUA and address the issues raised by the RAC. The motion was accepted by a vote of thirteen in favor, three opposed, and four abstentions.

B. Proposal to employ Harvey Sarcoma Virus as a vector.

Dr. Berns outlined a proposal (tab 793) from Dr. Malcolm Martin of the National Institutes of Health. He said that Dr. Martin proposes to employ defective Harvey Sarcoma Virus (HSV) as a vector. Defined sequences derived either from reverse transcription of messenger RNAs or specific viral segments would be inserted. Dr. Martin proposes to use the ability of sarcoma virus to transform to show that the defective genome has been picked up and is being expressed. Dr. Martin will co-infect with helper viruses in certain instances but not when the insert is a sequence from a second virus. Dr. Martin requests permission to perform this experiment at the P2 level. Dr. Baltimore said this request is analogous to a request which he had submitted several meetings previous. That proposal had been approved at the P2 level of containment. Dr. Goldstein asked what specific sequences would be inserted into the HSV vector. Dr. Martin responded that globin, some immunoglobin sequences and sequences from papovaviruses would be inserted. He said those experiments performed with papovavirus DNA will not employ helper virus. After Dr. Martin left the room, Dr. Baltimore moved approval

of the proposal as requested. The RAC accepted Dr. Baltimore's motion by a vote of thirteen in favor, none opposed and six abstentions.

Dr. Zaitlin noted that at the last RAC meeting the committee had approved a series of procedures, one of which requested submittors of proposals to provide a summary and to state how their proposal relates to existing Guidlines. Dr. Zaitlin asked whether ORDA has a mechanism to implement this procedure. Dr. Gartland responded that ORDA would ask investigators to write a summary in somewhat less technical terms, and to cite the applicable section of the Guidelines.

VIII. PROPOSED AMENDMENT OF SECTIONS I-A and II-D OF THE GUIDELINES

Dr. Novick said that the question that he raises here (tab 773B, 774/3) deals with the philosophical basis of the Guidelines. He said that the Guidelines were originally formulated on the hypothesis that recombinant DNA technology could result in the production of novel types of organisms. He said that as the properties of these novel organisms could not be predicted, a system was implemented wherein all such molecules would be contained. He observed that there has been a gradual change in the working philosophy of the RAC. He said the operative principle has become that prior restraint will not be imposed on scientific experimentation in the absence of fairly well defined hazard. Dr. Novick stated that he believed the committee should define its operating principle and insert that language into the Guidelines. He said he was not totally convinced that the exact language he had proposed for insertion into the Guidelines was appropriate, but that something to this effect should be inserted. Dr. Nightingale and Dr. Young objected to the wording of Dr. Novick's proposal.

Dr. Campbell said that if the motion as it now stands would be brought to a vote, he would strongly oppose it. The Guidelines would then state their purpose as dealing with cases of "clear perceived hazard." But that statement would then be followed by a long set of rules based on no clear perception of hazard.

Ms. King said it is still too soon in common law development to propose a fundamental shift in the underlying philosophy and assumptions of the Guidelines. She suggested that in order to debate this issue the RAC must be presented with very carefully drafted language. Dr. Novick said he would attempt to draft other language.

IX. PROTOCOLS REQUIRING ASSIGNMENT OF CONTAINMENT LEVELS.

A. Request for Containment levels for the cloning of Anabaena DNA into Klebsiella.

Dr. Brill introduced a proposal (tab 770, 774/8, 794) submitted by Dr. Robert Haselkorn of the University of Chicago. This had been discussed at the previous RAC meeting where it was not accepted pending further information. Dr. Brill stated that Dr. Haselkorn has cloned Anabaena DNA in plasmid pBR322 in E. coli. He said that Dr. Haselkorn would now like to transform this DNA into Klebsiella pneumoniae mutants that are defective in genes responsible for nitrogen fixation. Dr. Brill said Dr. Haselkorn indicates that the strain of Anabaena he proposes to use does not produce any toxins. Dr. Brill moved that Dr. Haselkorn's request be approved at P2+HV1 containment. Dr. Novick said that the concept of HV1 should not be included in the motion. The RAC has instituted fairly elaborate procedures to establish an organism as an HV1 host and that procedure is not being followed here. Dr. Young agreed.

Dr. Walters noted that Dr. Haselkorn requests permission to use a conjugative plasmid containing recombinant DNA. Dr. Maas said that the conjugative plasmid to be used to transfer the nitrogen fixation genes has been used around for years. Dr. Brill said that he sees no danger. He added that the experiment investigates a very important research area. Dr. Walters asked how many times the RAC has approved proposals using a conjugative plasmid. Dr. Setlow said the RAC had approved the use of the Ti plasmid of Agrobacterium tumefaciens in certain experiments. A motion to approve the request at P2 containment was accepted by a vote of twelve in favor, none opposed, and four abstentions.

B. Proposal to clone the Exotoxin A gene of Pseudomonas aeruginosa in E. coli.

Dr. Brill presented tab 792. This proposal from Dr. C. W. Shuster of Case Western Reserve University School of Medicine deals with Pseudomonas aeruginosa, which produces an exotoxin. Dr. Shuster would like to study the regulation of this exotoxin. Dr. Brill said that he supports this request.

It was pointed out that since Pseudomonas aeruginosa is on the Appendix A exchanger list, this experiment would be exempt from the Guidelines, except that the prohibitions override the exemptions and Section I-D-2 prohibits "deliberate formation of recombinant DNAs containing genes for the biosynthesis of toxins potent for vertebrates." Dr. Novick asked whether exotoxin A would be considered a potent toxin for vertebrates. Dr. Young responded that this question revolves about the interpretation of "potent." He said exotoxin A is clearly a toxin, but is not as potent as diphtheria toxin. Dr. Williams said he felt that exotoxin A is a potent toxin on the basis of the LD50 given on page 2 of tab 792.

Dr. Gottesman asked what type of containment is appropriate for this experiment. Dr. Young said he would recommend P3+EK2 since this appears to be an exception to a prohibition and containment should be assigned in a prudent and conservative manner.

Dr. Gottesman said she is not certain that P3+EK2, containment should be required, but the RAC should regard this request as a exception to a prohibition. It was agreed to republish this specific request in the Federal Register prior to its reconsideration at the next RAC meeting. Dr. Setlow also appointed a working group consisting of Drs. Maas, Brill and Campbell to consider this general issue.

C. Proposal to transform tobacco protoplasts with corn zein protein DNA ligated to the Ti plasmid of Agrobacterium tumefaciens.

Dr. Setlow absented herself and appointed Mr. Thornton as the chair in her absence. Dr. Zaitlin said that Dr. Setlow as chairman of Brookhaven National Laboratory local IBC has requested that the RAC consider a proposal from Dr. Benjamin Burr (771). Dr. Burr proposed to make cDNA for the corn protein, zein. The DNA will be cloned in a lambda vector and characterized. That piece of DNA will then be linked to the Ti plasmid of Agrobacterium and introduced into a plant protoplast with the expectation that they will grow into plants. Dr. Zaitlin said that Section III-C-4 of the Guidelines allows this proposal at P2 containment as requested. A motion that this proposal is covered by the current Guidelines was accepted by the RAC by a vote of seventeen in favor, none opposed and one abstention.

X. PROPOSED EK2 HOST-VECTOR SYSTEMS

Dr. Campbell began the presentation of tab 768, 774/9, 797 from Dr. P. Tiollais of the Institut Pasteur. He said that the RAC adopted at its May 1979 meeting a proposal from the Phage Subcommittee which specified that any Host-Vector system which has been certified as EK2 by the counterpart of the RAC in another nation, under criteria comparable to those set by RAC, may be processed as a minor modification following approval by the Phage Subcommittee. He said this request, therefore, does not have to be a RAC agenda item. Dr. Campbell said that the Subcommittee will proceed to review the request. Dr. Gottesman asked whether this proposal will revert to a major action if the Phage Subcommittee decides the information supplied by Dr. Tiollais is insufficient. Dr. Campbell said it probably would. Dr. Gottesman moved that these vectors be considered by the Phage Subcommittee as a minor modification under the clause concerning host-vector systems certified by foreign countries. Dr. Gartland asked Dr. Gottesman whether her motion actually designated these vectors as minor modifications. Dr. Gottesman responded that her motion proposed only they be considered under the clause dealing with foreign certified vectors. The RAC approved this motion by a vote of nineteen in favor, none opposed and no abstentions.

XI. PROPOSED AMENDMENT OF SECTION I-E OF THE GUIDELINES

Dr. Goldstein introduced tab 774/1. He said that the proposal stipulates that local IBCs be informed of exempt recombinant DNA experiments and upon request provide ORDA with a summary of these experiments. Mr. Thornton added that this motion grew out of a close vote at the last RAC meeting as to whether any notice or record of exempt experiments should be required. He added that the proposal provides for an informal but effective way of maintaining some record of exempt experiments. He said a parallel can be drawn to two other agencies, the National Science Foundation and the United States Department of Agriculture, which have reporting procedures for exempt experiments. Dr. Walters asked for an an estimate of the fraction of recombinant DNA work that is presently exempt. Dr. Setlow said that from her experience as chairman of a local IBC she would estimate 50%. Dr. Young said his experience suggests that it is 60%. Dr. Setlow added that this proposal, if enacted, would add an enormous burden on an already overburdened local IBCs.

Ms. King drew the parallel between the Institutional Review Board (IRB) and the IBC. She said that the committees should

focus on real hazards and that their effectiveness is short circuited to the extent that they are overloaded. Dr. Krimsky said the amount of extra effort on the part of the local IBC would be minimal. He said it is a matter of filing a list with the IBC chairman. The proposal doesn't stipulate that the IBC evaluate or review any of the experiments, nor does it say anything about the IBC having to produce the information except for an ORDA request. Dr. Krimsky said that in the event of an outbreak epidemiologists may find such a registry useful.

Dr. Young said that he opposes this motion. He is opposed to adding one more level of paper work which does not provide any safety function. Dr. Walters said that the proposal introduces an unnecessary disproportion between the rules that apply to recombinant DNA research and the rules that apply to other types of research. Dr. Ahmed moved approval of the proposal. The RAC disapproved this motion by a vote of five in favor, ten opposed, and four abstentions.

XII. AGENDA

Dr. Setlow suggested that the RAC continue on into the next day's schedule. Dr. Ahmed asked whether it is fair to advance items so much on the agenda. Dr. Pauker of NIOSH pointed out that there are non-voting liaison representatives that handle many other matters for their agencies. These representatives may wish to attend the discussion of some specific items and they will determine from the published agenda when issues of importance to them are going to be discussed. Ms. King said that the RAC is a public meeting and one of the criteria of a public meeting is a published agenda. She said the RAC should not make changes in the agenda without notification. Mr. Thornton suggested that future agendas should indicate that the agenda may be changed. Drs. Young and Mason suggested future agendas contain a statement that the time of consideration of specific items is only an approximatation. Dr. Setlow said she sensed the sentiment to be for adjournment. The RAC then adjourned for the day.

XIII. PROPOSED AMENDMENT OF SECTION III-B-2, III-C-5, III-C-6, AND III-C-7-a OF THE GUIDELINES

Dr. Gottesman presented the submission of Dr. David Hogness of Stanford University (tab 766, 774/4). Dr. Gottesman said that the language of Sections III-B-2, III-C-5, and III-C-6 of the Guidelines requires that a lambdoid phage vector or an approved EK2 vector be used for certain experiments involving "return of

DNA to host of origin." The use of these vectors was stipulated so that a small and fairly well defined amount of E. coli DNA would be returned to the host of origin. She said Dr. Hogness requests an amendment to to this language to permit any EK1 vector be used and returned with cloned DNA to the host of origin in Sections III-B-2, III-C-5 and III-C-6. She said this amendment would permit greater flexibility while not affecting safety and recommended that the RAC accept this proposal.

During this discussion, Dr. Young noted that some of the EK2 and EK1 vectors carry antibiotic resistance markers, and he cited the prohibition against introducing antibiotic resistance traits into prokaryotes. It was agreed that if an experiment falls under prohibition I-D-5, the prohibition overrides. Dr. Young said a specific question is whether introducing a recombinant vector made in E. coli into strain X to test whether antibiotic resistance is expressed is permissible. Dr. Campbell said that he thought this issue should be considered by the Plasmid Subcommittee. Dr. Setlow agreed and asked the Plasmid Subcommittee to study it. Dr. Maas said that the Plasmid Subcommittee should also address the question of using E. coli K-12 carrying conjugative plasmids as a host.

Dr. Gottesman moved that the RAC accept the language suggested by Dr. Hogness for Sections III-B-2, III-C-5, and III-C-6. The RAC accepted this change by a vote of fifteen in favor, none opposed, and three abstentions.

Dr. Gottesman began the presentation of the second part of Dr. Hogness's proposal (tab 774/5) to amend Section III-C-7-a to include invertebrates. She said that the RAC had approved under the Guidelines the transfer of DNA from any nonprohibited source to cells in tissue culture or into vertebrate nonhuman animals. She said the RAC's discussion at that time dealt extensively with what the modes of escape of recombinant DNA might be. In response to that discussion the RAC limited the amount of viral DNA which could be introduced to one quarter of the viral genome. She said the second question considered was whether the animal itself would escape. In response to this issue, the RAC limited cloning to vertebrates with the idea that vertebrates could be contained better than invertebrates, such as Drosophila. Dr. Gottesman said that Dr. Hogness requests this section now be extended to all non-human animals. Dr. Gottesman moved that the RAC reject this request as the question of escape remains relevant. The RAC accepted Dr. Gottesman's motion a vote of fifteen in favor, two opposed and two abstentions. Dr. Maas requested that he be recorded as voting opposed.

XIV. PROPOSED EXPIRATION OF SUPPLEMENT FOR VOLUNTARY COMPLIANCE

At the beginning of this discussion, Dr. Krimsky said that he would like to make available to the working group evaluating the FMD experiments, documents reporting on an outbreak of Foot and Mouth Disease on Plum Island in 1978.

Dr. Krimsky said that this proposal by Dr. Novick (tab 773A and 774/2) suggests that a trial period with an expiration date of June 1, 1980, be mandated for the voluntary compliance program for non-federally funded research. He said the RAC is saddled with review functions under the voluntary compliance program despite its recommendation that a mandatory program is needed. He pointed out that it is impossible to know which firms are carrying out recombinant DNA work in the absence of a mandatory registration process. He said the notion of voluntary compliance raises difficult questions: (1) How would a violation be reported and to whom? (2) Can the biosafety officer of a firm or its biosafety committee act independently? (3) Is not the greater hegemony of commercial over academic institutions a factor in the potential effectiveness of its biosafety committee? (4) If a firm openly violated the Guidelines, how should or would NIH respond? (5) What sanctions are available to restrain firms that flaunt the Guidelines or good microbiological practices? Dr. Krimsky stated that each of these queries represents a serious defect in a voluntary compliance scheme. He said the program of voluntary compliance could engender a sense of false confidence in the public at large. He called the committee's attention to tab 800, a letter from Senator Adlai Stevenson which concludes with a very strong statement that voluntary registration provides no assurance that all firms will register their research nor that any single firm will register all of its work.

Dr. Krimsky said that in the states and local communities that debated the issues, voluntary compliance by industry was not considered a viable option. He said that if one believes that there are any potentially real hazards either due to the techniques themselves or because the technique will increase substantially industry's use of biological agents, then one must take seriously the issue of regulation. Dr. Krimsky said he opposes Dr. Novick's motion because it presupposes that it can be ascertained whether a voluntary program of compliance is a success. Dr. Krimsky proposed the following alternative motion:

"Whereas a compliance program for non-NIH funded institutions undertaking large scale recombinant DNA activities based exclusively on the good faith of such institutions, involving no sanctions, and no accountability for breaches in compliance is untenable in concept, (1) RAC opposes the continuation of NIH's voluntary compliance program, and (2) RAC opposes its own use for reviewing protocols for large scale experiments for non-NIH funded firms until a mandatory compliance program is implemented, and (3) RAC reaffirms to the Director, NIH, its support for uniform standards."

Dr. Novick said that he basically agrees with Dr. Krimsky's position but he does not think that the option of opposing voluntary compliance is presently available. He suggested that if the RAC adopts this type of proposal, industry is invited to ignore the Guidelines. He said the purpose of his proposal is to indicate that the RAC is not satisfied with voluntary compliance as a permanent state of affairs.

Mr. Thornton said industry would wish to comply with the NIH Guidelines for several practical reasons: (1) Industry would like to have the approval of the NIH and of RAC for this type of research, (2) There are strong indications from other agencies that a failure to conduct research in accordance with NIH Guidelines will result in either a failure to be licensed or the possibility of not being able to protect proprietary information, and (3) Industry would wish to protect itself against civil sanctions. He said he opposes Dr. Novick's proposal.

Dr. Walters said that he is in sympathy with Dr. Novick's proposal but would prefer to stipulate that at the June 1980 meeting the RAC review the voluntary program rather than state that the program will terminate at that time.

Dr. Goldstein read a section of the Minutes of the May 25, 1979 meeting of Peter Libassi HEW General Counsel with representatives of the Pharaceutical Manufacturers Association: "Peter Libassi, however, noted the press reports of some companies not complying with the NIH Guidelines. The article in Nature regarding Genentech, Inc. (a non-PMA firm) was cited. Bill Gartland reported that Genentech had told NIH they were proceeding with certain experiments that were not in compliance. Further, they had stated orally that they would proceed notwithstanding NIH objections. Mr. Libassi felt that Genentech should be put on

notice in some formal way that this was unacceptable behavior, perhaps in a letter from Dr. Fredrickson or the Secretary. It was noted that some drug companies have contracts with Genentech. It might be helpful, Mr. Libassi pointed out if they insisted that all their contractees adhere to the NIH Guidelines. The PMA representatives agreed to work for industrial compliance."

Mr. Thornton asked Dr. Gartland to comment. Dr. Gartland said that his statement yesterday concerning Genentech and their scale up in October of 1978 under the 1976 Guidelines is accurate. He said the May 25, 1979 Minutes cited above are not precise. Dr. Ross said that Genentech did not have a representative at that meeting. Dr. Novick said he did not think the May 25, 1979 Minutes germane to the issue before the RAC. Mr. Thornton asked if Genentech had said they were in violation and would continue in violation. Dr. Gartland and Dr. Ross said that they had not.

Dr. Goldstein said that the RAC had previously passed a motion recommending mandatory regulation. Dr. Walters pointed out that the vote on this recommendation was 9-6-6. He said that the interagency committee which Dr. Fredrickson had convened agreed with the voluntary compliance scheme. Dr. Ahmed said favored uniform standards and uniform regulations. Dr. Adams of PMA said that industry has indicated its willingness to abide by the Guidelines. He pointed out that the RAC is proposing an action to consider the expiration of a section of the Guidelines that is still only proposed. Dr. Johnson of Eli Lilly stated that the term voluntary is a misconception, as industry is under constant monitoring by a large number of regulatory agencies. Dr. Adams said that PMA firms are subject to inspection by OSHA relative to biohazards.

Mr. Thornton said that three procedural options are open to the RAC: (1) Dr. Krimsky's motion could be adopted. Presumably, the RAC would not review further large-scale proposals, (2) The RAC could accept voluntary compliance until such time as Congress adopts a law establishing mandatory compliance, or (3) The RAC could propose a reevaluation of the its role after aquiring some experience in the application of voluntary compliance.

Ms. King said that she is opposed to voluntary compliance as the mode of regulation applied to academia should be the same as applied to industry. She said she none the less supports Dr. Novick's motion because it provides the opportunity to evaluate voluntary compliance after acquiring some experience. Ms. King stated that tort sanctions work. Researchers are very concerned about their prestige and their status in the profession.

She said that withdrawal of funds has never been a particularly effective sanction. Dr. Campbell said withdrawal of funds is indeed an effective sanction against universities. Ms. King responded that the sanction is so severe that there is enormous reluctance on the part of the government to use it.

Dr. Novick said that the purpose of his motion was not so much to evaluate the effectiveness of voluntary compliance but more to put the committee on record as affirming its motion that mandatory compliance is desirable. Dr. Young said that he would like to restate the position of the American Society for Microbiology. He then read a letter of October 19, 1979, addressed to Dr. Fredrickson from the Committee on Genetic and Molecular Systemic Microbiology of the American Society for Microbiology Board for Public and Scientific Affairs (Attachment II).

Dr. Goldstein suggested that the following wording be substituted for (3) in Dr. Krimsky's motion:

> "That the RAC recommends to the Secretary of HEW that Federal legislation rather than voluntary compliance is required for the regulation of non-Federally funded research in the area of recombinant DNA research."

Dr. Krimsky accepted the proposed amendment. Dr. Young proposed an amendment that would delete the preamble which reads as follows:

> "Whereas a compliance program based exclusively on the good faith of such institutions, involving no sanctions, and no accountability for breaches in compliance, is untenable in concept."

Dr. Krimsky accepted the proposed amendment. The Krimsky motion as amended failed by a vote of five in favor, nine opposed and four abstentions. Dr. Goldstein requested that his vote in favor be recorded.

Dr. Novick moved 774/2 with the addition of item 3 of the previous motion as amended by Dr. Goldstein. Ms. King said the proposal is now inconsistent. Paragraph 1 of 774/2 states that it is desirable to establish a uniform standard of conduct for the performance of experiments involving recombinant DNA techniques while the new added paragraph specifies the type of uniformity that is required. This motion was defeated by a vote of seven in favor, ten opposed and two abstentions. Dr. Goldstein asked that his vote in favor of the motion be recorded.

Ms. King moved the motion as it appeared in the Federal Register (774/2). Dr. Gottesman proposed to amend the last paragraph of the proposal to read as follows:

> "At the same time, the committee regards the concept of voluntary compliance as experimental; in order to ensure further consideration after an initial trial period, the Committee agrees to conduct a review of the voluntary compliance program at its June 1980 meeting."

Dr. Zaitlin favored this amendment which would eliminate the reference to a June 1, 1980, termination data. Dr. Novick said he preferred to retain a termination date in the proposal. The RAC accepted Dr. Gottesman's amendment by a vote of ten in favor, seven opposed and one abstention. A vote on 774/2 as amended by Dr. Gottesman was accepted this motion by a vote of fourteen in favor, three opposed and one abstention.

The text of the motion as adopted by the RAC is as follows:

> "Whereas it is desirable to establish a uniform standard of conduct for the performance of experiments involving recombinant DNA techniques,
>
> And whereas the RAC has recommended mandatory compliance with the NIH Guidelines for non-federally funded institutions,
>
> And whereas there is currently no extent legal framework within which this can be effected,
>
> The RAC congratulates the Pharmaceutical Manufacturers Association and its member companies for the cooperative spirit that they have shown in agreeing to comply with the NIH Guidelines voluntarily under provisions of the supplement to the Guidelines adopted by the RAC at its meeting of September 6-7, 1979.
>
> At the same time, the committee regards the concept of voluntary compliance as experimental, in order to ensure future consideration after an initial trial period, the committee agrees to conduct a review of the voluntary compliance program at its June 1980 meeting.

XV. RISK ASSESSMENT.

A. Report on Status of Risk Assessment.

Dr. Krause said that the final risk assessment plan was published in the Federal Register of September 13, 1979, and NIAID is attempting to implement that plan. NIAID has two continuing intramural activities on risk assessment: (1) evaluation of polyoma virus cloned in E. coli host-vector systems and (2) studies on the biological activity of E. coli K-12 carrying DNA copies of RNA tumor viruses.

Dr. Krause said the NIAID had convened a small ad hoc group chaired by Dr. Stanley Falkow on August 30, 1979, to consider implementation of the Falmouth protocols. He said that group recommended that there be a study of the HS strain of E. coli to study the transmission of plasmid pBR325 to the intestinal flora in normal humans. Dr. Krause reported that NIAID has issued a request for proposals aimed at developing resources for a modular training course for microbiological techniques including the development of self-study aids.

Dr. Nutter then summarized briefly the progress of risk assessment contracts. He said there are presently three contracts applicable to risk assessment. (1) The contract with Dr. Sagik at the University of Texas at San Antonio will terminate in June. Its purpose is to test EK1 and EK2 systems for their survival in sewage treatment plant models. (2) The second contract is with Dr. Rolf Freter at the University of Michigan. That contract is scheduled to expire in March 1980. EK1 and EK2 systems are being tested for their survival in mice and in special culture conditions. (3) The third study is at Tufts University which is scheduled to expire December 1979. Dr. Stuart Levy has been testing EK1 and EK2 strains in humans and mice.

Dr. Young said plasmid transfer to anaerobes which comprise most of the bowel flora, was an important question as transfer of an E. coli plasmid into Bacteriodes fragilis by conjugation has been reported.

Dr. Krause then reported on the joint meeting between a NIAID ad hoc working group and the RAC Risk Assessment Subcommittee. The invited consultants included Dr. Louis Sherwood, an endocrinologist and peptide hormone biochemist of the Department

of Medicine, Michael Reese Hospital and Medical Center, and Dr. Philip Patterson who is professor of microbiology and immunology at Northwest University Medical and Dental Schools.

Dr. Krause summarized the report of the meeting (Attachment III). The meeting was concluded with an agreement that the following initiatives will be undertaken: (1) All of the risk assessment data on E. coli K-12 including the evidence concerning possible colonization will be drawn together as rapidly as possible and made available for review by all interested parties. (2) A small group of individuals will be brought together to discuss possible risks that might be associated with E. coli K-12 producing biologically active peptides including hormones. (3) A second small group of individuals will be convened to discuss the possible risks arising from immunological events that might be initiated by E. coli K-12 that are producing eukaryotic polypeptides including hormones. Dr. Krause said that NIAID would like to move as rapidly as possible to convene these groups. Dr. Krause said NIAID will hold the meeting at a time when the largest number of knowledgeable people can attend. An invitation will be extended to all RAC members.

Dr. Goldstein asked that two documents dealing with the biology of E. coli be made available to the RAC. These are articles by Dr. Stanley Falkow and Dr. Roy Curtiss. Dr. Goldstein requested that Dr. Falkow be invited to attend the next RAC meeting. Dr. Goldstein asked whether the question of rheumatic fever had been raised at that NIAID meeting. Dr. Krause said that one possibility studied for many years is that rheumatic fever is an aberrant immunological reaction to Streptococcol infection. He said it is true that there are Streptococcol antigens cross reactive with mammalian tissue but there is no evidence that antibodies to these are involved in pathogenesis. However, very few infected individuals develop rheumatic fever.

B. Proposed amendment of Section I-D of the Guidelines.

Dr. Gottesman began this presentation (tab 774/10). She said the proposal suggests that experiments prohibited by Sections I-D-1, I-D-2, I-D-3 and I-D-5 and experiments involving "wild type" host-vector systems be excepted from the prohibition

provided the experiments are designed for risk assessment and are conducted within the NIH high-containment facilities. These containment facilities are Building 41-T on the campus and in Building 550 located at the Frederick Cancer Research Center. The selection of laboratory practices and containment levels for such experiments would be approved by ORDA following consultation with the RAC Risk Assessment Subcommittee and the NIH Biosafety Committee. Dr. Gottesman said that the principle is justifiable and the containment appears high enough to bypass any potential problems. Dr. Gottesman then moved acceptance of the proposal as written. Dr. Nightingale questioned whether some provision should stipulate that after data are evaluated, there should be destruction of any hazardous materials generated.

Dr. Young proposed the following amendment to the proposal:

> "If a major biohazard is determined, the clones will be destroyed after the completion of the experiment rather than retaining them in the high containment facility. Other clones that are not hazardous or not of major hazard will be retained in high containment."

Dr. Gottesman accepted his amendment. Dr. Novick said he did not see the necessity for risk assessment experiments involving the introduction of antibiotic resistance traits which would compromise medical or veterinary therapy. He suggested that reference to Section I-D-5 be struck from the proposal. Dr. Campbell disagreed. Similarly, Dr. Young said that the understanding of antibiotic resistance is so important that it should be permitted in a very high containment facility. Dr. Gottesman suggested that the RAC vote on Dr. Novick's amendment to delete Section I-D-5. The RAC denied this motion by a vote of three in favor, thirteen opposed and three abstentions. Drs. Novick and Goldstein requested that they be recorded as voting in favor of the amendment.

Dr. Ahmed said that he would like to amend the motion by adding language requiring that all RAC members be notified prior to beginning the experiments. Dr. Barkley suggested that the amendement be worded as follows:

"ORDA shall inform RAC members of proposed risk assessment projects at the same time it seeks consultation from the RAC Risk Assessment Subcommittee and the NIH Biosafety Committee."

Dr. Ahmed said that was the sense of his motion. Dr. Gottesman accepted this amendment. The RAC then voted on 774/10 as published in the Federal Register with Dr. Young's amendment and Dr. Barkley's amendment. The vote was seventeen in favor, one opposed and no abstentions. Dr. Novick requested that he be recorded as voting opposed.

The text of the motion adopted by the RAC to be added at the end of Section I-D of the Guidelines is as follows:

"Experiments in Categories I-D-1, I-D-2, I-D-3, I-D-5, and experiments involving 'wild-type' host-vector systems are accepted from the prohibitions, provided that these experiments are designed for risk assessment purposes and are conducted within the NIH high-containment facilities located in Building 41-T on the Bethesda campus and in Building 550 located at the Fredrick Cancer Research Center. The selection of laboratory practices and containment equipment for such experiments shall be approved by ORDA following consultation with the RAC Risk-Assessment Subcommittee and the NIH Biosafety Committee. ORDA shall inform RAC members of the proposed risk-assessment projects at the same time it seeks consultation from the RAC Risk-Assessment Subcommittee and the NIH Biosafety Committee. If a major biohazard is determined, the clones will be destroyed after the completion of the experiment rather than retaining them in the high containment facility. Other clones that are non-hazardous or non-hazardous or not of major hazard will be retained in the high containment."

C. Proposed amendment to permit use of CDC Class 3 agents.

Dr. Talbot noted that this item (767) had not appeared in the Federal Register prior to the meeting and cannot be formally

acted upon at this meeting. Dr. Mason said this proposal, originating with NIAID, requests a change in the Guidelines to permit experimentation with CDC Class 3 agents. If approved, experiments with these agents would be removed from the prohibited category. Dr. Krause said that NIAID is initiating this request because of its programmatic interest and responsibilities for developing new modalities of prevention of infectious diseases. He said for these experiments NIAID suggests a transfer from prohibited to permissible under uniform P3+HV1 conditions. He noted that there are major research opportunities, which could eventually lead to new and better methods of diagnosis, treatment, and prevention. He suggested that the RAC form a working group to establish a position on Class 3 agents. Dr. Novick said he strongly favors this proposal but noted that several questions might be raised. If this proposal is approved, prohibitions, I-D-1, will only cover a few viruses in Class 4 and 5. Dr. Gottesman said that there are several problems a working group would have to work out in order to include Class 3 agents under permissible experiments and yet be consistent with the rest of the Guidelines.

Dr. Ahmed questioned the rational for proposing P3 containment. Dr. Nutter said Class 3 organisms are investigated in this country and abroad under P3 conditions. Dr. Goldstein said he would like someone to address the question of whether the host range of these organisms might be altered. Dr. Gottesman said that her understanding of the proposal is that DNA from Class 3 organisms would be permitted to be introduced into HV1 organisms. The proposal is not permitting DNA to be introduced into Class 3 organisms. Dr. Setlow appointed Dr. Young, Dr. Mason and Dr. Novick to a working group to consider this issue.

XVI. PHYSICAL CONTAINMENT GUIDELINES FOR LARGE-SCALE USES OF ORGANISMS CONTAINING RECOMBINANT DNA MOLECULES

Dr. Walters presented the draft proposal of the working group on large-scale (tab 774/7 and 790). He noted that the members of the Working Group were Emmett Barkley, Sheldon Krimsky, Frank Young and himself. He added that Robert McKinney of Enviro Control contributed as a consultant. Dr. Walters said that no equivalent physical containment large-scale standards are available in other countries. He said the proposed Guidelines extrapolate

from the Guidelines for research with smaller volumes. He said that a policy decision was made that representatives of public interest groups or representatives of industry would not be consulted during the initial development of the standards. As the standards are now in draft form, comments from interested parties or groups would be welcomed.

Dr. Barkley said that the large scale standards employ an extension of the philosophies and concepts behind the Guidelines for laboratory scale experimentation. The format of Section II-B was followed with emphasis on those activities that relate to large scale. Primary emphasis is placed on the vessels used for the production of large volumes. These vessels are self contained and capable of providing excellent primary containment. The working group emphasized the need for active certification of the containment features of the vessels before use in large scale production.

Dr. Young said that he was concerned with one aspect of the safety features, namely whether a simple plug or stop of the primary drain in the fermentor apron is adequate. He said he would recommend a requirement for an additional valve that could be turned off below any drain within the apron. He noted that such a valve would aid in decontamination.

Dr. Gottesman asked why the working group had specified P2 and P3 levels of large-scale containment when not every large scale growth of a recombinant molecule is going to require that level of containment. Dr. Walters replied that the design of large facilities ordinarily provides greater than P1 containment. Dr. Gottesman said that she is concerned that the RAC will spend time evaluating trivial, very safe, proposals. Dr. Gottesman stated that proposals absolutely without hazard should be handled in a simpler fashion.

Dr. Ahmed noted that there is no provision for P4 containment in the large scale standards. Dr. Gottesman said that she did not think any project which would require P4 would be approved for large scale growth.

Dr. Barkley noted that the draft standards require procedures for inactivating accidental spills. Dr. Wright said that whereas one sort of laboratory procedure would suffice for small spills

a different approach might be required with a large spill. Dr. Novick questioned whether an architectural barrier is required. Dr. Johnson of Eli Lilly summarized some key points in his detailed comments (tab 806) on the large-scale proposal. He said there should be a P1-LS containment level. Architectural curbs are not necessary. He enumerated some of the specific suggestions.

Dr. Campbell said that once a project is approved on a pilot scale, scale-up to a larger facility should not require detailed reconsideration by the RAC. The RAC should indicate in the original approval whether the properties of the organism would give cause for concern should a large amount be worked with.

Dr. Myers of NIOSH said that his agency will evaluate the draft standards. He noted that he has several questions on the Laboratory Procedures section. Dr. Krimsky suggested that procedures to monitor worker-health should be specified for large-scale experiments. Dr. Wright said that in the United Kingdom there is industry and trade union representation on GMAG.

Dr. Walters requested that the RAC authorize ORDA and the working group to actively solicit comments from public interest groups, industry, Federal agencies, organizations of workers, GMAG, and other organizations concerning the draft standards. Mr. Thornton so moved and the RAC accepted this motion by a vote of fifteen in favor, none opposed, and no abstentions. Based on the comments received the draft standard will be revised and considered again at the March 1980 meeting.

XVII. CLOSED SESSIONS

The RAC went into closed session to consider proposals from commercial concerns for scale up of recombinant DNA experiments.

XVIII. FURTURE MEETING DATES

The RAC selected the following dates for future meetings:

March 6-7, 1980

June 5-6, 1980

XIX. ADJOURNMENT

The meeting was adjourned at approximately 5:15, December 7, 1979.

Respectfully submitted,

Elizabeth A. Milewski, Ph.D.
Rapporteur

William J. Gartland, Jr., Ph.D.
Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date

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National Institutes of Health

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MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTE OF HEALTH

TO : The Record

DATE: December 6, 1979

FROM : Director, NIAID

SUBJECT: Meeting of Working Group to Discuss Further Activities Pertaining to Risk Assessment of Recombinant DNA Research

The working group met on December 5, 1979 at 1:00 p.m. in the Terrace Room of the Linden Hill Hotel. A list of the invited participants is attached. Dr. Richard M. Krause, Director, National Institute of Allergy and Infectious Diseases chaired the meeting.

The working group consisted of RAC Members, including Dr. Setlow, Chairman of RAC and Mr. Ray Thornton, Chairman of the RAC Subcommittee on Risk Assessment. In addition, two outside consultants were present who have had special experience in peptide hormone chemistry and physiology, immunology and auto-immunity. These were Dr. Louis Sherwood, Chairman, Department of Medicine, Michael Reese Hospital and Medical Center and Dr. Philip Paterson, Chairman, Department of Microbiology - Immunology, Northwestern University Medical and Dental Schools.

The purpose of this meeting was to focus on the two areas of risk for which there is still concern in some quarters. These were presented by the RAC Subcommittee to the RAC in September. It was suggested at that time a conference be planned as expeditiously as possible on the following areas:

1. Studies of hormone producing strains of E. coli to evaluate direct adverse effects.

2. Possible occurrence of auto-antibodies or auto-reactive cells due to the production of eukaryotic polypeptides (including hormones) by bacteria that colonize organisms.

In advance of this meeting the participants had been sent a series of background documents. These included:

1. Final plan for a program to assess the Risk of Recombinant DNA Research.

2. Proceedings of the workshop held at Falmouth, Massachusetts on June 20-21, 1977.

3. Report of the U.S. EMBO Workshop to assess Rick for Recombinant DNA experiments involving the genomes of animal, plant and insect viruses.

4. Copies of correspondence to Dr. Wallace Rowe concerning the possibility of immunological disease and the effects of active proteins.

5. The memorandum of September 4, 1979 from Chief, OSRF, NIAID summarizing the major recommendations of an ad hoc NIAID Working Group on Risk Assessment.

After introductory remarks describing the administrative arrangements as well as the process which has led to the current Risk Assessment Program, both before and after this became the responsibility of NIAID, Dr. Krause then proposed that the meeting review first the process which has been employed in the past to develop Risk Assessment experiments which are appropriate to the issues in question, and then move to a consideration of the major matters on the agenda.

Dr. Malcolm Martin reviewed the process of developing the content and the format of the Falmouth and the Ascot conferences. He indicated that in the development of such conferences there is a need to develop and analyze hypothetical scenarios pertaining to risk within the context of recombinant DNA experiments. Major underlying considerations are the larger public health issues which are involved in this work. He emphasized also that a conference on risk should allow a thorough and brisk exchange of views by individuals with broad backgrounds from diverse disciplines which bear on the issues of the recombinant DNA technology. These issues include the potential benefit of the technology, and the infectious disease implications, particularly identifying issues in regard to infectious disease pathogenesis as well as the epidemiology and ecology of bacteria including E. coli K-12.

Dr. Sherwood then discussed various aspects concerning possible adverse effects from hormone producing E. coli K-12. He began with general comments concerning the overall issues pertaining to recent research on the chemistry and physiology of biologically active peptides and hormones. He noted, for example, that hormones are produced by "ectopic" tissues in some cases which had not been expected. Thus, many ectopic tumors are now recognized as sources of unexpected hormone production. He noted that the occurrence of such adventitious hormone production may make it difficult to determine if a putative active peptide is attributable to bacterial colonization or to ectopic tissue. Then too, the site of production by

the bacteria would alter possible risks, hormones secreted into the surrounding media would be a bigger problem than those produced in the cytoplasm. Cleaved or uncleaved states were other factors.

Dr. Sherwood noted that there is an extremely wide range of active peptides that could potentially have adverse effects if the E. coli synthesizing them did in fact either colonize the intestinal tract or cause an infection or abscess of soft tissue. The view was expressed that there is less risk of absorbtion of active peptides from the intestinal tract, and probably a greater risk of leakage of a peptide from an E. coli abscess or infection. In the discussion which followed several additional aspects of these matters were raised. Little is known, for example, about the transport of active peptide hormones across the intestinal lumen into the blood stream in the young infant. Yet it is known that in infants proteins such as those in cow's milk and antibodies in human breast milk pass from the intestine into the blood stream. It is also not clear if active peptides produced in an E. coliK-12 abscess would be degraded by the proteolytic autolysis in the abscess, or would diffuse to any significant extent into the circulation. Dr. Sherwood concluded his remarks by saying that the issue really centers on the assessment of the risk that E. coli K-12 can or cannot colonize, cause soft tissue infections, or abscesses.

It was pointed out by Dr. Krause that there was a considerable body of evidence to suggest that E. coli K-12 did not colonize the intestinal tract of man or experimental animals although there was some evidence that there was carriage for a week or more in some instances as a large dose of E. coli K-12 were washed out with the passage of the intestinal contents. Such statements, however, are made on the basis of some information which has yet to be published and therefore, it has not been possible for all interested parties to assess all of the facts concerning colonization of the intestine by E. coli K-12.

Several RAC members felt that it was important to learn from the endocrinologists the dose of insulin as well as other hormones that have adverse effects. It would also be important to know what are the limits of tolerance to an excess of hormone production for a limited period. Dr. Sherwood said that there was information on these questons and that such data could be pulled together.

Dr. Philip Paterson discussed some of the issues pertaining to the possible occurrence of auto-antibodies or auto-reactive cells due to the production of eukaryotic polypeptides (including hormones) by bacteria that might colonize higher organisms.

Dr. Paterson limited the bulk of his remarks to the issues pertaining to cross-reactivity between a bacterial product and an antigen of mammalian tissue, and the possibility that such cross reactivity might result in auto-antibodies that would produce an immunological disease. He began by noting that there are, in fact, many examples of serologic cross reactions between polysaccharides and protein antigens of existing microorganisms and mammalian tissue antigens. There is considerable evidence that many of these bacterial antigens and, indeed antigens from other sources, do give rise to natural antibodies that cross react with antigenic determinants of mammalian tissue. The evidence is sparse, however, that such cross-reactive antibodies are directly involved in the so called auto-immune diseases, or to put it another way the evidence is sparse that the bacterial antigens are the stimulus of those auto-antibodies that are in special cases directly involved in the auto-immune processes. Dr. Paterson cited a number of examples from clinical medicine to illustrate the fact that well known cross reactions do not appear to lead to a disease process. He noted, for example, that there are antigens in the tubercle bacillus which cross react with a protein glycolypid component in myelin and yet there is no clinical evidence that patients with tuberculosis have an increased incidence of neurological diseases.

Dr. Paul indicated that the immunological questions were not limited to the issue of auto-immunity and cross reactivity. Dr. Asofsky made the point that there are possible issues concerning immune reactions to foreign substances. Dr Paul, for example, indicated a worse possible case scenario would be the production of antibodies to acetyl choline receptors as a consequence of an immune response to this substance elaborated by E. coli K-12.

Again, in these discussions on potential immunological risks the issue came back to an assessment of the capacity of E. coli K-12 to colonize or be converted to a potential pathogen? Can it produce an abscess or soft tissue infections?

While it was noted the risks are minimal with E. coli K-12, possible risk associated with plasmid transfer from E. coli K-12 to a wild type was an issue that raised the need for a discussion of an evaluation of risk assessment with wild type E. coli.

While no scenarios were developed, the notion was expressed by several that it may be time to consider carefully the first steps that should be taken in risk assessment with wild type E. coli as this pertains to Recombinant DNA Research. While any experiments of this nature would fall into the prohibited category, a request could be made to the RAC for an exemption so that such risk experiments could be performed.

Page 5 - Risk Assessment of Recombinant DNA Research

The meeting was concluded with an agreement that the following initiatives will be undertaken.

1. All of the risk assessment data on E. coli K-12 including the evidence concerning possible colonization will be drawn together as rapidly as possible and be made available for review by all interested parties.

2. A small group of individuals will be brought together to discuss the possible risks that might be associated with E. coli K-12 producing biologically active peptides including hormones.

3. A second small group will be convened to discuss the possible risks arising from immunological events that might be initiated by E. coli K-12 that are producing eukaryotic polypeptides including hormones.

At both of these meetings there will be a thorough background presentation of the current evidence concerning the risk assessment studies performed thus far with E. coli K-12, as well as the evidence documenting its attenuated nature as a pathogen.

Richard M. Krause, M.D.

AGENDA
NIAID WORKING GROUP
December 5, 1979

1:00	Opening Comments	Dr. Krause
1:20	Consideration of Autoimmunity and Identification of Scientific Issues	Dr. Paterson
2:30	Consideration of Active Peptides and Identification of Scientific Issues	Dr. Sherwood
3:30	Discussion of Conference Objectives, Format and Scope	Dr. Campbell
4:00	Development of the Group's Recommendation to NIAID	Mr. Thornton

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October 19, 1979

Dr. Donald S. Fredrickson, Director
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780

Dear Dr. Fredrickson:

The Committee on Genetic, Molecular, and Systematic Microbiology of the American Society for Microbiology Board of Public and Scientific Affairs recommends the following in regard to regulations of recombinant DNA investigations:

1. Restrictions in the Guidelines should be revised downward as the evidence for lack of biohazards becomes apparent and justifies it.

2. The Committee recommends the procedures for notification and approval of recombinant DNA work be streamlined. Workers should be able to modify protocols within the original intent, without the need for resubmission of NUAs.

3. The Committee endorses the efforts by the NIH to extend the Guidelines to the private sector and has confidence in the way they are handling these matters. We recommend that the RAC be expanded to include members with expertise in industrial microbiology.

4. We recommend that experiments in excess of 10 liters should be approved on a case by case basis. In this connection, we recommend that the members of panels have appropriate expertise by education, experience, and training to evaluate what is done. We believe the panel should include members with expertise in industrial microbiology and with familiarity in large scale containment operations.

5. We remind you that ASM takes the position that training is another line of defense. Mechanisms should be established to ensure that investigators using recombinant DNA technology have adequate training on the principles and techniques of acceptable microbiological practice to achieve containment objectives.

Sincerely,

Harlyn O. Halvorson

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